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REVIEW ARTICLE

Water and electrolyte homeostasis during decongestion in heart failure

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In heart failure, sodium retention generally occurs out of proportion to water retention and may occur disproportionate to chloride retention, requiring excretion of other cations (i.e. potassium, magnesium, and hydrogen). Renal homeostatic mechanisms keep chloride levels in balance, making it the primary regulator of intravascular tonicity. Excess total body sodium stores and potassium depletion increase the vulnerability to dehydration, especially in the intracellular compartment. With decompensation, extracellular volume expansion with sodium and chloride overload occurs, further enhancing potassium losses. While diuretics are vital to treat fluid overload, they derange important electrolyte and water balances. Diuretic therapies in heart failure produce disproportionate electrolyte-free water excretion, further exacerbate potassium depletion, and cause chloride losses disproportionate to natriuresis. This can be mitigated by allowing liberal electrolyte-free water intake, providing aggressive potassium and chloride supplementation, and using upfront proximal diuretics to preserve the chloride balance.

Keywords Chloride • Diuretics • Heart failure • Homeostasis • Potassium • Sodium

Introduction

Diuretics are a cornerstone in the management of heart failure (HF) with fluid overload, to alleviate symptoms of congestion and preserve organ function.[1,2] Although their clinical utility is undeniable, their complete physiological effects remain insufficiently appreciated, with scarce attention paid to the complex interplay of water and electrolyte homeostasis during decongestive treatment. It is crucial to recognize that while diuretics might be effective to achieve fluid removal, they do not always do so in a manner that preserves or restores homeostasis. Indeed, diuretic therapies may cause electrolyte abnormalities, renal dysfunction, neurohumoral activation, and worsening sodium (Na^+) avidity.[3,4]

A wealth of data has reported significant impact on Na^+, chloride (Cl^-), and potassium (K^+) levels through diuretic therapies. Most commonly employed diuretic schedules in HF cause hypokalaemia and disproportionate Cl^- losses that may lead to hypochloraemia, with both electrolyte disorders being associated with increased mortality.[5–7] Additionally, loop diuretics and acetazolamide facilitate the loss of electrolyte-free water, which may lead to dehydration, especially in the context of stringent fluid restriction. These alterations in fluid and electrolyte dynamics reflect the inherent challenges to tailoring diuretic therapy and produce balanced diuresis in HF with fluid overload.

In this review, it is argued that diuretic therapy may significantly disrupt electrolyte and water homeostasis if not counterbalanced with appropriate therapeutic strategies. Three key observations are made: (i) HF pathophysiology is characterized by Na^+ retention that is disproportionate to electrolyte-free water retention and results in reduced total body K^+ stores as well; (ii) diuretic therapy leads to disproportionate excretion of electrolyte-free water, further exacerbates K^+ depletion, and causes a Cl^- loss that is out of proportion to natriuresis; and (iii) to counterbalance this mismatch between HF pathophysiology and necessary diuretic treatment, it is critical to allow adequate electrolyte-free water intake, provide aggressive K^+ supplementation, and preserve the Cl^- balance. The goal of this review is to equip the clinician with the fundamental physiological principles to understand electrolyte disturbances during the treatment of acute HF with diuretics and emphasize the importance to achieve 'balanced' diuresis to restore homeostasis.

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Electrolyte and water homeostasis in heart failure

Heart failure is associated with characteristic changes in total body Na^+, K^+, Cl^-, and electrolyte-free water, which are further influenced by diuretic therapies (*Figure 1*).

Sodium and water

Sodium and water retention in heart failure

Excessive salt and water retention leading to an inappropriate volume expansion of the intravascular and interstitial space, is a hallmark feature of the HF syndrome that is already present early on in its pathophysiological development.[8] Experiments that mostly predate the contemporary treatment era of HF have used radio-nuclear tracer dilution methods to quantify total body water (TBW) and total exchangeable Na^+ ($TENa^+$) in patients and healthy volunteers.[9–16] The total exchangeable amount of an electrolyte represents the physiologically active pool that dynamically participates in exchange between extracellular and intracellular compartments, excluding the inert reserves stored in bone or cartilage. Studies have confirmed that both TBW and TENa+ are increased in subjects with HF who have signs of fluid overload when compared to healthy controls (37.5–43.6 L vs. 29.6–35.0 L and 3583–4291 mmol vs. 2105–3129 mmol, respectively) (online supplementary *Figure Appendix S1* and *Table Appendix S1*).

Intriguingly, it seems that Na^+ retention occurs out of proportion to increased TBW in HF. While the $TENa^+$/TBW ratio is consistent around 80–85 mmol/L in healthy controls, a markedly higher ratio is observed in HF (91–108 mmol/L) (online supplementary *Figure S2* and *Table Appendix S1*). Farber and Soberman[10] have demonstrated that the $TENa^+$/TBW ratio is also greater in HF when compared to other oedematous conditions such as the nephrotic syndrome and cirrhosis. Importantly, even though subjects with HF but without oedema had similar TBW compared to healthy controls, their $TENa^+$ and $TENa^+$/TBW ratio remained clearly elevated, suggesting a state of relative dehydration (online supplementary *Figures Appendix S1* and *S2* and *Table Appendix S1*). Considering the average $TENa^+$ (3941 mmol in HF with oedema vs. 2835 mmol in healthy controls) and average TBW (38.5 L in HF with oedema vs. 34.2 L in healthy controls) from all available studies, patients with HF seem to retain 257 mmol of Na^+ for every 1 L excess TBW.[10,11,15] Remarkably, this significantly exceeds the Na^+ concentration in serum or the interstitial compartment (i.e. 135–155 mmol/L), suggesting an important buffer capacity. Anand *et al.*[15] have estimated that >85% of the increase in TBW of subjects with HF compared to healthy controls was accounted for by an increase in extracellular water (ECW), which is the compartment that has Na^+ as its primary cation. This was true even though the extracellular compartment in absolute size remained smaller than the intracellular compartment, with ECW accounting for 42% of TBW in healthy controls versus 48% in subjects with HF. If water retention would have been the primary pathophysiological culprit, a more equal distribution across intracellular water (ICW) and ECW would be expected. These findings suggest that Na^+ retention and accumulation in the extracellular space seems to be the central pathophysiological culprit in HF, whereas water retention is most likely a secondary phenomenon that aims to preserve serum and tissue osmolality. Indeed, although arginine vasopressin (i.e. antidiuretic hormone) levels that regulate water homeostasis are elevated in patients with HF compared to healthy volunteers, their linear relationship with serum osmolality is generally well-maintained.[17] In other words, oedematous states such as HF are caused by exaggerated Na^+ retention, whereas dysnatraemias result from impaired water handling. Importantly, $TENa^+$ (representing physiologically active Na^+ stores in the body) is fundamentally different from serum Na^+ concentration, which primarily reflects the water content in the vascular space only. Indeed, patients with HF exhibited a broad range of serum Na^+ concentrations despite uniformly elevated $TENa^+$/TBW ratios.[13] Interestingly, those with more pronounced hyponatraemia even had the highest $TENa^+$ levels.

Role of intracellular and interstitial sodium buffering

It may seem surprising that $TENa^+$ increases in such excess compared to TBW in HF, despite minimal disruptions in extracellular osmolality. Four plausible mechanisms could explain this observation. It remains unclear to what extent each factor plays a role.

1. *Extracellular water expansion*: any increase in ECW/TBW increases $TENa^+$/TBW as well, as the large majority of Na^+ remains in the extracellular compartment. Using the weighted data from the available literature (online supplementary *Table Appendix S1*) and assuming Na^+ concentrations of 150 and 10 mmol/L in the ECW and ICW, respectively, an increase in $TENa^+$ equal to 617 mmol (i.e. 615 mmol in the ECW and 2 mmol in the ICW) is expected. Nevertheless, this leaves 489 mmol of the observed 1106 mmol (44%) $TENa^+$ increase unexplained.
2. *Intracellular water shrinkage*: as ECW = TBW-ICW, ECW/TBW may increase as well when ICW shrinks. Although weighted data from the available literature suggest an average 0.2 L ICW increase, it is not unthinkable that some patients may experience some intracellular volume contraction. Experimental data indeed suggest that salt loading induces a metabolic shift towards a water-preserving catabolic state, which is associated with a reduction in total body cell mass (as an endogenous source of water) and a reduction in ICW.[18]
3. *Intracellular Na^+ shift*: some of the excess Na^+ may move to the intracellular compartment in exchange for K^+, magnesium or hydrogen ions (which are subsequently excreted). Increased intracellular Na^+ levels up to 30 mmol/L have been demonstrated in the muscles, skin, and circulating cells of both experimental models of HF and patients with HF.[19,20]
4. *Extracellular Na^+ buffering*: a last potential explanation may be volume-independent extracellular Na^+ buffering. Large, negatively charged polysaccharides called glycosaminoglycans are present in bones, cartilage, skin and the luminal side of the endothelium, where they may act as a Na^+ scavenger preventing its osmotic activation.[21] The ability to adaptively vary glycosaminoglycan concentration and sulfation patterns (which

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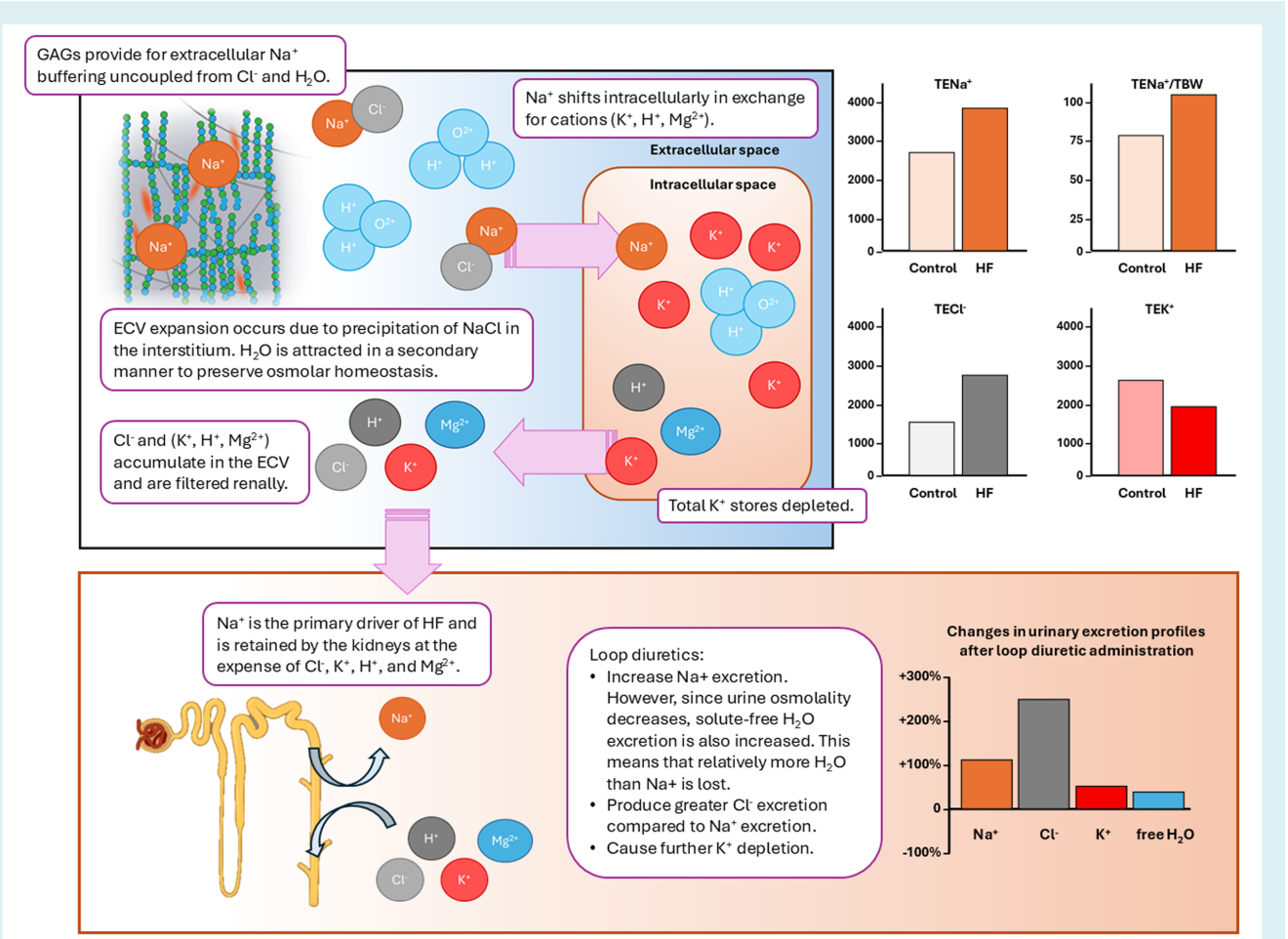
GAGs provide for extracellular Na+ buffering uncoupled from Cl- and H2O.
Na+ shifts intracellularly in exchange for cations (K+, H+, Mg2+).
Extracellular space
Intracellular space
ECV expansion occurs due to precipitation of NaCl in the interstitium. H2O is attracted in a secondary manner to preserve osmolar homeostasis.
Cl- and (K+, H+, Mg2+) accumulate in the ECV and are filtered renally.
Total K+ stores depleted.
TENa+
TENa+/TBW
TECl-
TEK+
Control
HF
Na+ is the primary driver of HF and is retained by the kidneys at the expense of Cl-, K+, H+, and Mg2+.
Loop diuretics:
• Increase Na+ excretion. However, since urine osmolality decreases, solute-free H2O excretion is also increased. This means that relatively more H2O than Na+ is lost.
• Produce greater Cl- excretion compared to Na+ excretion.
• Cause further K+ depletion.
Changes in urinary excretion profiles after loop diuretic administration
+300%
+200%
+100%
0
-100%
Na+
Cl-
K+
free H2O

Figure 1 Integrated summary of pathophysiological mechanisms in heart failure (HF) and the effect of loop diuretics. Renal sodium (Na^+) retention is the key pathophysiological feature of HF, leading to an increased ratio of total exchangeable Na^+ ($TENa^+$) over total body water (TBW). Na^+ accumulation occurs through mechanisms coupled and uncoupled with chloride (Cl^-) and water (H_2O). The coupled mechanism involves precipitation of NaCl in the interstitial compartment, attracting H_2O to preserve osmolar homeostasis (i.e. [subclinical] oedema). The uncoupled mechanisms are: (1) extracellular buffering by glycosaminoglycans (GAGs); and (2) intracellular shift of Na^+ in exchange for cations such as potassium (K^+), protons (H^+), and magnesium (Mg^{2+}). This exchange displaces Cl^-, K^+, H^+, and Mg^{2+} towards the extracellular volume (ECV), where homeostasis is maintained by the kidneys and those electrolytes are excreted. Loop diuretics increase both Na^+ and solute-free H_2O excretion, resulting in more H_2O than Na^+ being lost. In addition, loop diuretics result in greater Cl^- compared to Na^+ excretion and further exacerbate K+ depletion.

encode location and activity of these proteins) in the skin and endothelium may play a role in osmo- and volume regulation. Higher interstitial glycosaminoglycan contents have been found on skin biopsies in patients with HF versus healthy volunteers, which was associated with markers of neurohumoral activation and attenuated by implementation of guideline-directed medical therapies.[22] Finally, ^{23}Na-cardiac magnetic resonance studies have confirmed Na^+ accumulation in the interstitial compartment of patients with HF, although it is difficult to prove whether this is buffered Na^+ or subclinical oedema.[23]

Importantly, electro-neutrality should be preserved in each of these scenarios. While Na^+ and Cl^- are obviously coupled in changes of the ECW or ICW, Na^+ accumulation in excess of Cl^- may occur with an intracellular shift or extracellular buffering. This would require an exchange with other cations such as K^+ and magnesium or the production of acid (i.e. proton release) that may subsequently be excreted, mainly through urine.

Intracellular dehydration

Intracellular water can only be indirectly assessed by subtracting ECW from TBW. In the study by Anand *et al.*,[15] less than 15% of increased TBW in HF was due to an increase in ICW, while in some patients ICW may actually have shrunk. Several osmole transporters and signalling cascades tightly maintain the intracellular volume within safe limits. However, the higher interstitial solute load makes patients with HF at higher risk of intracellular dehydration, especially when oral intake is poor or solute-free water is lost in

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excess such as with diarrhoea, sweating, or diuretic use. This is also supported by the fact that urine osmolality in patients with HF tends to be at the higher end of the normal spectrum (i.e. ~800 mOsm/kg) in an attempt to retain as much solute-free water as possible.[24] A recent analysis of the DAPA-Shuttle1 trial provides further support for this hypothesis of dehydration in HF, as the expected glucose-driven osmotic diuretic potential of dapagliflozin was eliminated by physiologically adaptive water conservation, preventing an increase in urine output in euvolaemic patients.[25] Intracellular dehydration, which might be assessed by serum osmolality promotes thirst, neurohumoral activation, and therefore diuretic resistance in HF.

Potassium

Lower potassium stores in decompensated heart failure

Potassium is crucial to maintain normal cellular function. The transmembrane potential difference is sustained by the K^+ gradient that is actively regulated by the ubiquitous Na^+–K^+–ATPase. This gradient underpins vital processes such as muscle contraction and nerve conduction. Additionally, K^+ plays a key role in the regulation of the intracellular volume and maintenance of acid–base equilibrium. Total body K^+ is approximately 50 mmol per kg of body weight, yet only 2% of K^+ resides in the extracellular compartment.[26] For a 70 kg person, this would correspond to a total body K^+ of 3500 mmol, with 70 mmol in the ECW. There are radio-nuclear tracer dilution methods as well to quantify total exchangeable K^+ (TEK^+). Studies have demonstrated decreased TEK^+ in subjects with HF and signs of fluid overload when compared to healthy controls[11–14,27] (online supplementary *Table Appendix S1*). Furthermore, while the $TEK^+/TENa^+$ ratio is consistent at 0.75–1.00 in healthy controls, a significantly lower ratio is observed in HF, especially when oedema is present, with values ~0.50 (online supplementary *Figure S3A* and *Table Appendix S1*). Thus, while K^+ stores seem to be preserved or slightly reduced in compensated HF, they are significantly reduced in decompensation.

The role of body composition on potassium stores

Low dietary intake of K^+, use of K^+-losing diuretic drugs, and neurohumoral activation may all contribute to a total body K^+ deficit in HF. However, a change in body composition with loss of lean body mass and/or fat mass due to cachexia, physical inactivity, chronic inflammation may alternatively explain the lower TEK^+. Through measuring TBW, ECW and TEK^+ simultaneously, Moore *et al.*[28] showed that the intracellular K^+ concentration remains stable across a range of conditions associated with reduced TEK^+, such as starvation and chronic wasting illness. Furthermore, Birkenfeld *et al.*[11] and Lye[29] found that there was no longer a difference between patients with HF and healthy controls when TEK^+ was indexed to dry body weight or fat-free mass. Moreover, similar reductions in TEK^+ are known to accompany aging and a number of other critical or chronic disease states that result from a loss of lean body and/or fat mass.[30] Nevertheless, as suggested above, the replacement of intracellular K^+ by Na^+ in HF pathophysiology may deprive total body K^+ stores.

Hypokalaemia in heart failure

Low total body K^+ is not necessarily synonymous with hypokalaemia because K^+ shifts from the intracellular compartment may stabilize plasma levels. Nevertheless, the fact that patients with HF have a lower TEK^+ implies a lower buffer capacity to adequately adapt to acute fluctuations in K^+ availability. Among 5848 patients with HF from the observational Swedish Heart Failure (SwedeHF) registry, 20.3% developed at least one episode of hypokalaemia (<3.5 mmol/L) and 3.7% developed severe hypokalaemia (<3.0 mmol/L).[31] Acute hospitalization, diuretic use, more severe HF, and comorbidities such as chronic kidney disease, atrial fibrillation, and chronic obstructive pulmonary disease were all significant predictors of hypokalaemia and seem to describe a phenotype with decreased TEK^+.

Several acute triggers may precipitate hypokalaemia in patients with HF. Secondary hyperaldosteronism, which is especially prevalent in worsening HF, is likely an important mechanism, as aldosterone promotes K^+ secretion at the distal convoluted tubules and collecting ducts of the nephron. Use of loop and/or thiazide-like diuretics increases Na^+ delivery to the distal nephron, further promoting K^+ loss, as Na^+ reabsorption in this segment is achieved in exchange of K^+ secretion. Additionally, loop and thiazide-like diuretics cause Cl^- loss that causes metabolic alkalosis, which leads to intracellular translocation of K^+ and even lower plasma levels.[32,33] Finally, the recommended daily dietary K^+ intake (90–120 mmol) is rarely met in patients with HF, especially in the elderly, those with chronic kidney disease, and those following a Western diet.[34]

Impact of hypokalaemia on prognosis in heart failure

Several epidemiological studies have associated hypokalaemia with worse clinical outcomes in diverse populations, although this not necessarily implies a causal relationship.[7] Importantly, even serum K^+ values in the low normal range (i.e. 3.5–4.0 mmol/L) have been associated with a higher risk of all-cause mortality, cardiovascular mortality, and HF hospitalization, with optimal levels determined at 4.2–4.4 mmol/L. Being a marker of more severe disease, low serum K^+ levels themselves may also lead to morbidity and mortality in several ways. While an increased risk of cardiac arrhythmias is often thought to be the primary mechanism, this may only account for a minority of cases. In an observational study of 2164 patients with chronic HF that found a relationship between lower serum K^+ and mortality, 50.4% died during a median follow-up of 2.8 years, yet only 7% of those deaths were attributed to sudden cardiac death.[35] Several lines of research support a contributing role of (even subclinical) hypokalaemia in HF progression through myocardial dysfunction, peripheral muscle dysfunction, impaired vasodilatation and hypertension, atherosclerosis and vascular inflammation, and renal ischaemia.[36–41] An impaired cardio-renal response to salt loading via dysregulated signalling in the with no lysine (K) kinase-sterile20 related proline-alanine-rich kinase/oxidative stress response kinase 1 (WNK-SPAK/OSR1) pathway appears to be a key mechanism driving the adverse effects of hypokalaemia[42] (*Figure 2*). Low extracellular K^+ disrupts K^+–Cl^- cotransporters that reduce intracellular Cl^- levels, which in turn activate the

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Cl^--sensitive WNK kinases. Activation of WNK-SPAK/OSR1 signalling leads to upregulation of the Na^+/Cl^- symporter (NCC), located in the distal tubules to promote Na^+ reabsorption and contribute to hypertension and fluid retention. This mechanism is illustrated by Gordan syndrome (or pseudo-hypoaldosteronism type II), which is characterized by gain-of-function mutations in the WNK-SPAK/OSR1 signalling pathway and presents with salt-sensitive hypertension due to the upregulated NCC.

Chloride

Total body chloride in heart failure

Finally, also total exchangeable Cl^- ($TECl^-$) can be determined through radio-nuclear tracer dilution methods.[13,14,27] In patients with HF and extracellular fluid overload, $TECl^-$ is slightly increased, as would be expected because osmotically active Na^+ and Cl^- are coupled to maintain electro-neutrality (online supplementary *Figure S3B* and *Table Appendix S1*). Importantly, the kidneys monitor volume status through sensing of Cl^- rather than Na^+ in the macula densa cells lining the tubular system at the end of Henle's loop, which is coupled to neurohumoral activation.[43] This explains why serum Cl^- levels are strongly defended by the body's homeostatic mechanisms, even at the cost of disturbances in the Na^+, K^+, or water equilibrium. Indeed, while at the level of the kidney Na^+ and Cl^- retention are generally coupled, both electrolytes play a completely different role in osmo- and volume regulation.

Chloride, volume homeostasis and acid–base balance

There is an interesting and often underappreciated relationship between Cl^-, volume homeostasis and acid–base balance, which is most easily understood using the physicochemical approach for acid–base disorders (i.e. Stewart method). The physicochemical approach defines the strong ion difference (SID) as the difference between fully dissociated cations (i.e. primarily Na^+ in plasma) and anions (i.e. primarily Cl^- in plasma). The SID is a key determinant of the plasma hydrogen concentration (pH). In plasma, the SID or simplified difference between serum Na^+ and Cl^- is approximately 40 mmol/L (or 140–100 mmol/L). As specified by the physicochemical approach, any SID increase causes alkalosis, while any decrease leads to acidosis. Isotonic or hypertonic NaCl loading increases ECW, but at the same time decreases the SID (as the SID of NaCl is 0 because of equal amounts of Na^+ and Cl^-), resulting in metabolic acidosis.[44] Interestingly, the same holds true for dietary NaCl intake.[45] Conversely, disproportionate Cl^- losses compared to Na^+ increase the SID, leading to hypochloraemic metabolic alkalosis. This effect is well-illustrated in cystic fibrosis, where excessive Cl^- losses in sweat predispose to metabolic alkalosis, especially with hypovolaemia.[46]

In HF, neurohumoral activation promotes NaCl retention and relative hyperchloraemia, which thus decreases the SID to promote metabolic acidosis. This in turn leads to renal vasoconstriction and a shift of K^+ from the intra- to the extracellular compartment. The latter occurs as Na^+ enters the cell in exchange for K^+, a process driven by inhibition of Na^+–K^+–ATPase activity. At the same time, homeostatic renal mechanisms try to maintain a normal Cl^- balance by excreting excess Cl^-. In HF, because of increased Na^+ avidity, urinary excretion of KCl is favoured over NaCl, resulting in K^+ depletion.[4] Thus, while $TECl^-$ may appear normal in compensated HF, disproportionate Na^+ loading through interstitial and intracellular buffering mechanisms increases the vulnerability to dehydration and acid–base disturbances, while promoting K^+ (and magnesium) losses. In decompensated HF, excess NaCl overwhelms the body's buffering capacity, leading to increased $TECl^-$, ECW expansion, and further intracellular K^+ depletion. This contributes to hyponatraemia and hypochloraemia that occur in patients with advanced HF and are further worsened by Cl^--losing diuretics.

Hypochloraemia and diuretic resistance

Hypochloraemia (serum Cl^- <96 mmol/L) occurs in 13–21% of patients with acute HF and is a major factor in the occurrence of diuretic resistance.[5] Low urine Cl^- concentrations (<115 mmol/L) in patients with acute HF indicate ongoing neurohumoral activation and are associated with poor net fluid balances and worse outcomes.[47] Several studies support the role of Cl^- as a key regulator of renal Na^+ avidity.[4] Decreased tubular Cl^- delivery to the macula densa promotes neurohumoral activation and increased proximal tubular Na^+ reabsorption through tubulo-glomerular feedback.[43] The Cl^--sensitive WNK kinases are also activated by hypochloraemia, promoting NCC expression in a K^+-independent manner[42] (*Figure 2*). Furthermore, Cl^- exerts a tonicity effect that tends to favour distribution of fluid from the interstitial space to the intravascular space. Conversely, hypochloraemia may result in a reduction of effective circulating volume.[48] Finally, Cl^- exerts allosteric regulation of epithelial Na^+ channels in the distal nephron, with higher Cl^- concentrations demonstrated to block access of Na^+ to the channel pore.[49]

Effects of diuretic therapy on water and electrolyte homeostasis

Under the ideal scenario, diuretic therapy would exactly reverse the electrolyte and water disturbances caused by HF: (i) restore normal total body Na^+ by inducing natriuresis; (ii) maintain normal Cl^- levels; (iii) regain K^+ losses; and (iv) prevent dehydration by inducing a greater solute than water excretion. However, one can easily appreciate that this is *not* what diuretics do in clinical practice (*Figure 3*). *Table 1* provides an overview of the different diuretic classes with their target effect, site of action, and effect on water excretion and electrolyte homeostasis.

Natriuresis

First, urine Na^+ concentrations that are 100–130 mmol/L with an optimal diuretic response are lower than serum Na^+ concentrations (i.e. ~140 mmol/L) and never get even close to the 257 mmol of excess $TENa^+$ per 1 L of TBW observed in HF.[50] Consider the hypothetical example of a 70 kg patient with HF who presents

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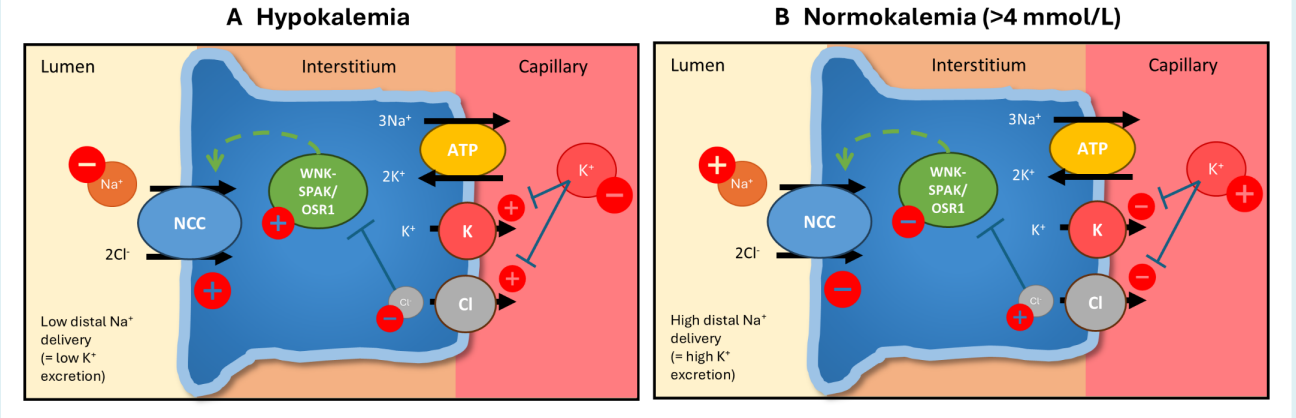

Figure 2 Relationship between serum potassium (K^+) concentration and sodium (Na^+) reabsorption at the distal tubule. (*A*) Hypokalaemia disrupts K^+-chloride (Cl^-) cotransporters to reduce intracellular Cl^- levels, which in turn activate the Cl^--sensitive with no lysine (K) kinase (WNK) kinases. Activation of WNK-sterile20 related proline-alanine-rich kinase/oxidative stress response kinase 1 (SPAK/OSR1) signalling leads to upregulation of the Na^+/Cl^- symporter (NCC) located in the distal tubules to promote Na^+ reabsorption and contribute to hypertension and fluid retention. (*B*) K^+ supplementation suppresses the WNK-SPAK/OSR1 pathway and downregulates Na^+ reabsorption through the NCC.

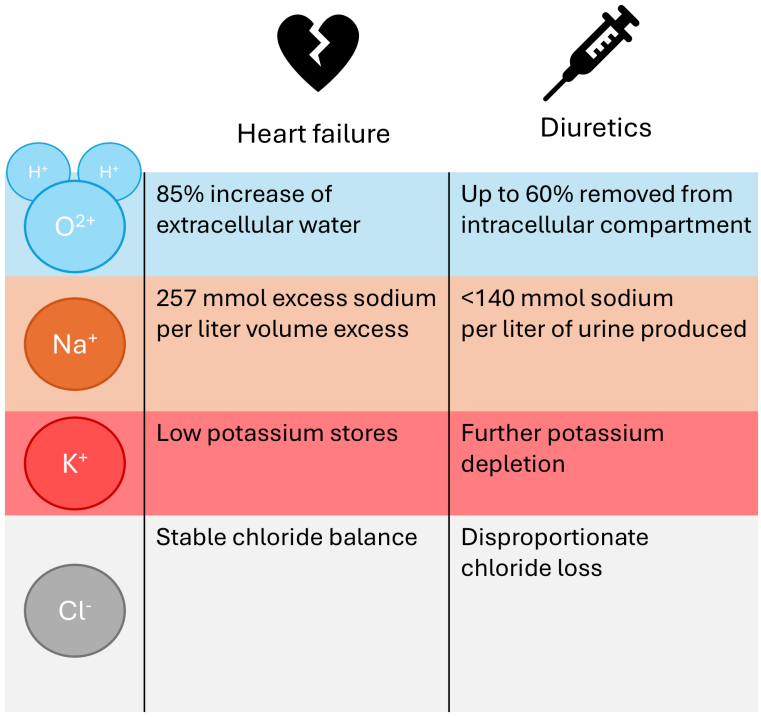

Figure 3 Mismatch between water and electrolyte disturbances in heart failure and the effects of commonly employed diuretic therapies.

with fluid overload and has an excess TBW of 3 L. The expected excess $TENa^+$ would be ~771 mmol (i.e. 3 × 257 mmol). However, even with an excellent diuretic response of 3 L urine with a Na^+ concentration of 120 mmol/L, still less than half of the excess $TENa^+$ would have been removed. To remove the remaining excess Na^+ without causing dehydration, electrolyte-free fluid intake or administration is needed. This explains why net negative natriuresis rather than a net negative fluid balance predicts outcomes better after an episode of decompensated HF.[51] It is key to realize that *natriuresis* rather than urine output alone is the goal of decongestion, as only removing Na^+ will have lasting effects on the ECW. This is because osmolality (i.e. 275–295 mOsm/L) is strongly

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Table 1 Diuretic classes with their target effect, site of action and effect on water excretion and electrolyte homeostasis

	Acetazolamide	SGLT2i	Loop diuretics	Thiazide-like diuretics	MRA/amiloride
Target effect	Inhibits the Na^+/H^+ exchanger through inhibition of carbonic anhydrase	Inhibits SGLT2	Inhibits NKCC	Inhibits NCC	Inhibits ENaC
Nephron segment	Proximal tubules	Proximal tubules	Loop of Henle	Distal convoluted tubule	Distal tubules and collecting ducts
Diuresis	++[a]	+[a]	++++	++	++
Free water excretion	+++	++	+++	–	–
Na^+ excretion	+[a]	(+)[a]	+++	++	++
K^+ excretion	++	(+)	+++	++	–
Cl^- excretion	–	0	+++	++	++
HCO_3^- excretion	+++	++	0	0	+

Cl^-, chloride; ENaC, epithelial sodium channel; H^+, proton; HCO_3^-, bicarbonate; K^+, potassium; MRA, mineralocorticoid receptor antagonist; Na^+, sodium; NCC, sodium–chloride symporter; NKCC, sodium–potassium–chloride cotransporter; SGLT2i; sodium–glucose cotransporter 2 inhibitor.
[a]Diuresis and sodium excretion may significantly increase when acetazolamide or SGLT2i are combined with more distal working diuretics.

protected by the homeostatic mechanisms of thirst that are largely preserved in HF.[17] Nevertheless, diuretic therapies tend to produce more of water diuresis than natriuresis.

Chloride balance

Commonly employed loop and thiazide-like diuretics in HF are associated with a disproportionate Cl^- loss. Scheen *et al.*[52] have demonstrated that urinary Cl^- excretion is increased by ~246% throughout a 24-h period after administration of furosemide 40 mg in subjects with HF, with the most pronounced increase up to 499% seen within 4 h. Importantly, the 24-h increase in urinary Cl^- excretion was much higher when compared to the effect on natriuresis (246% vs. 137%), which is remarkable considering that in patients with decompensated HF, actually more Na^+ than Cl^- needs to be removed. Similar results have been found in a contemporary cohort of patients with acute HF.[53] In addition, in a study using real-time urine electrolyte monitoring after furosemide administration in critically ill patients, natriuresis declined substantially after 1–2 h, while the increase in urinary Cl^- excretion was sustained for a much longer period.[54] Within 2 h after furosemide administration, the fractional excretion of Cl^- was greater than of Na^+ (9% vs. 7%). This difference may be due to an increase in aldosterone-mediated Cl^--independent Na^+ reabsorption and a reduction in Cl^- reabsorption via the Cl^-/bicarbonate exchanger pendrin in the lumen of the renal tubules.[55] This explains why diuretic therapy causes hypochloraemic metabolic alkalosis, as the SID is increased due to exaggerated Cl^- losses. Although often called 'contraction alkalosis', this term oversimplifies the underlying mechanism by attributing alkalosis primarily to volume depletion. In reality, metabolic alkalosis may happen as well with ongoing fluid overload and attenuates the efficacy of loop diuretics, implying that disproportionate Cl^- losses may be more important.[33]

Interestingly, in contrast to urine Na^+ concentrations, urine Cl^- concentrations after loop diuretic administration are often higher than those in plasma (i.e. ~140 mmol/L and ~100 mmol/L, respectively). Indeed, the $Na^+/K^+/2Cl^-$ symporter normally causes more Cl^- than Na^+ reabsorption, which is needed because tubular fluid at the end of the proximal tubules contains a relatively higher Cl^- content as some Na^+ is exchanged for protons in order to maintain acid–base equilibrium. Downstream, some Na^+ is exchanged for K^+, further exacerbating relative Cl^- losses in comparison to natriuresis. Thus, diuretics, when completely restoring Na^+ balance, risk to cause marked Cl^- depletion, which results in neurohumoral activation and diuretic resistance.[33]

Potassium depletion

While patients with HF, even when compensated, usually have low TEK^+, which markedly deteriorates during developing congestion, most diuretics further increase K^+ losses. This occurs by enhancing Na^+ delivery to the distal tubules and collecting ducts, where Na^+ is reabsorbed in exchange for K^+. In addition, increased tubular flow rate further promotes distal K^+ secretion. Urinary K^+ excretion is increased with ~30% throughout a 24-h period after administration of furosemide 40 mg in subjects with HF, with the most pronounced increase seen up to 150% within 4 h.[52] Importantly, the majority of K^+ is lost from the intracellular compartment, which is markedly underestimated by serum K^+ levels. Indeed, each 1 mmol/L decrease in serum K^+ levels represents a loss of TEK^+ that is approximately 200–400 mmol.

Dehydration

Diuretics increase solute-free water excretion through their effect on the kidneys. Data by Olesen *et al.*[56] demonstrate that urine osmolality may decrease from 800 mOsm/kg to 300 mOsm/kg and free water absorption may decrease from 1410 ml/24 h to 80 ml/24 h after administration of 4 mg of bumetanide. Thus, more than 1 L of solute-free water may be lost following a single dose of

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loop diuretics. Up to 60% of solute-free water removed through diuresis is lost from the intracellular compartment that is the least expanded in HF, with a minimal impact on blood volume.[57,58] This poses a further risk for intracellular dehydration in patients with HF when submitted to diuretic therapy.

While the solute-free water clearance reflects total water excretion, the electrolyte-free water clearance is even more relevant in clinical practice because it determines the impact of diuretic therapy on the serum Na^+ concentration. Unlike solute-free water clearance, which considers all osmolytes, electrolyte-free water clearance focuses only on Na^+ and K^+, the key electrolytes that determine the serum Na^+ concentration. Electrolyte-free water excretion equals the volume of urine output multiplied by $(1 - \frac{urine\ Na+ + urine\ K+}{serum\ Na+})$. If the sum of the urine concentrations of Na^+ and K^+ is smaller than the serum Na^+ concentration, the electrolyte-free water excretion is positive, and serum Na^+ will rise. Vice versa, when the urine concentrations of Na^+ and K^+ are greater than the serum Na^+ concentration, serum Na^+ will drop because of electrolyte-free water is retained.

Producing balanced diuresis with an appropriate decongestive strategy

Because of the obvious mismatch between water and electrolyte disturbances in HF and the effects of commonly employed diuretic therapies (*Figure 3*), some therapeutic strategies may be considered to produce more balanced diuresis and restore homeostasis (*Figure 4*). Therefore, careful monitoring of serum and urine electrolyte concentrations and osmolality during treatment for decompensated HF may help to optimize outcomes and minimize complications.

Liberal fluid intake

As explained, most patients with HF, even those with fluid overload, are in a relative state of dehydration, with less water excess than would be expected for their excess in total body Na^+. Up to half of patients with HF report significant distress due to thirst during hospitalization.[59] Osmolality regulation, governed by arginine vasopressin (i.e. antidiuretic hormone) and thirst mechanisms, is remarkably precise. Any increase in plasma osmolality – such as those resulting from renal Na^+ retention and elevated $TENa^+$ – therefore promptly activates thirst mechanisms. As osmoregulation remains intact in patients with HF,[17,25] the presence of thirst reflects an appropriate physiological response to relative dehydration. Therefore, during decongestive treatments, it makes sense to recommend fluid intake according to thirst, while electrolyte-free water supplementation may be considered in patients who are likely to respond insufficiently to thirst because of frailty or incapacitation. It seems reasonable to allow intake *ad libitum* as long as an overall net negative fluid balance is preserved in patients with clear signs of fluid overload. This also argues against the use of vasopressin antagonists like tolvaptan in decompensated HF, as they further worsen dehydration.[17] Although it may sound counterintuitive to allow or even administer more fluids in a patient with fluid overload, one should remember that the ultimate goal of decongestion is to durably reduce extracellular fluid overload through natriuresis, which may eventually require administration of water to prevent dehydration. Assessment of serum osmolality may help to assess hydration status. The recently published Fluid Restriction in Heart Failure versus Liberal Fluid Uptake (FRESH-UP) trial in patients with chronic HF provides further support for a liberal fluid intake, which did not result in a significant difference in health status versus fluid restriction up to 1500 ml per day, and lowered perceived thirst distress.[60]

Natriuresis-guided decongestion

Given that natriuresis is the primary goal of decongestion, there has been increasing interest in monitoring urine Na^+ concentration as an objective and readily available metric for diuretic response.[50] The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) and Pragmatic Urinary Sodium-based Algorithm in Acute Heart Failure (PUSH-AHF) studies have shown that systematic assessment of post-diuretic urine Na^+ concentration leads to the use of more intensive diuretic regimens that significantly increase natriuresis and potentially facilitate decongestion.[61,62] The recently presented, but not yet published DECONGEST study (NCT05411991) has also reported faster achievement of euvolaemia with natriuresis-guided decongestion, but this did not translate into a shorter length of hospital stay. None of these studies had a sufficient sample size for hard clinical endpoint evaluation, which should be the topic of a future trial. By adding information on the estimated glomerular filtration and urine creatinine concentration to urine Na^+ concentration, a natriuretic response prediction equation may be used to reliably predict natriuresis.[63] The Urine Chemistry Guided Acute Heart Failure Treatment (ESCALATE, NCT04481919) trial is testing this approach for a hierarchical composite endpoint of vital status, hospitalization status, need for intravenous diuretic treatment and general wellbeing during the first 14 days of the intervention.

Natriuresis-guided intensification of the diuretic regimen may encompass dose increases of loop diuretics or use of combination therapy with acetazolamide and/or thiazide-like diuretics in various combinations. Furthermore, early initiation and rapid up-titration of guideline-directed medical therapy in general and sodium–glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists in particular, is key to improve decongestion.[64] Direct Na^+ removal through peritoneal dialysis is also explored as an intriguing new decongestion strategy.[65]

Aggressive potassium repletion

As early as 1949, Fox *et al.*[66] observed that the administration of K^+ increased diuresis in patients with HF. This can be explained because K^+ suppresses the WNK-SPAK/OSR1 pathway and downregulates Na^+ reabsorption through the NCC (*Figure 2*). Preclinical models have demonstrated rapid dephosphorylation and deactivation of the NCC, leading to increased natriuresis following an oral K^+ load.[67,68] K^+-induced natriuresis has been demonstrated

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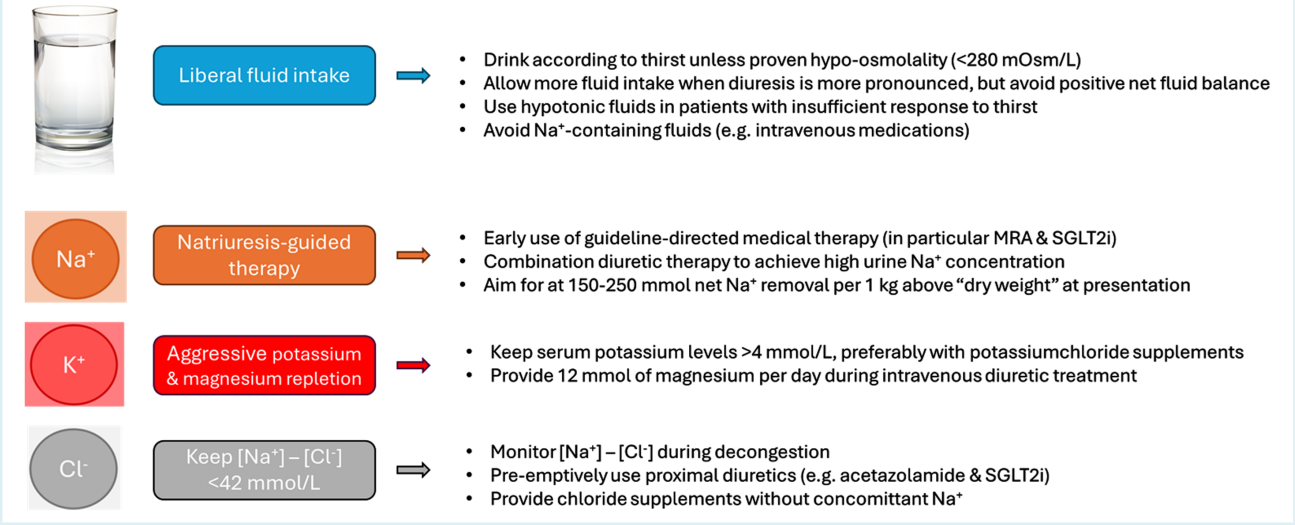
Liberal fluid intake
Drink according to thirst unless proven hypo-osmolality (<280 mOsm/L)
Allow more fluid intake when diuresis is more pronounced, but avoid positive net fluid balance
Use hypotonic fluids in patients with insufficient response to thirst
Avoid Na+-containing fluids (e.g. intravenous medications)
Na+
Natriuresis-guided therapy
Early use of guideline-directed medical therapy (in particular MRA & SGLT2i)
Combination diuretic therapy to achieve high urine Na+ concentration
Aim for at 150-250 mmol net Na+ removal per 1 kg above "dry weight" at presentation
K+
Aggressive potassium & magnesium repletion
Keep serum potassium levels >4 mmol/L, preferably with potassiumchloride supplements
Provide 12 mmol of magnesium per day during intravenous diuretic treatment
Cl-
Keep [Na+] – [Cl-] <42 mmol/L
Monitor [Na+] – [Cl-] during decongestion
Pre-emptively use proximal diuretics (e.g. acetazolamide & SGLT2i)
Provide chloride supplements without concomittant Na+

Figure 4 Practical recommendations during diuretic therapy in acute heart failure to avoid unbalanced diuresis resulting in electrolyte disturbances. MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

in humans as well.[69] Given that even subclinical K^+ depletion contributes to increased renal Na^+ avidity and adverse outcomes, it is prudent to pursue serum K^+ levels >4 mmol/L during decongestion. As a 30% increase in K^+ loss is expected during intravenous diuretic treatment, it is reasonable to provide 40 mmol of K^+ supplements on a daily base in patients with optimal K^+ levels 4–5 mmol/L. KCl should be preferred over other formulations (such as K-gluconate, K-citrate or K-bicarbonate), as it tackles disproportionate Cl^- losses induced by diuretic treatment at the same time and prevents exacerbation of metabolic alkalosis (which is promoted by each of the other formulations). Supplementation can be achieved via oral supplements or a maintenance infusion, such as 5% dextrose solution containing 3 g magnesium sulphate and 0–60 mmol KCl (adjusted to serum K^+ levels). Close monitoring of serum K^+ levels remains crucial, especially in those with poor diuretic response and/or severe kidney dysfunction.

Metabolic alkalosis, hyperaldosteronism, and magnesium depletion may render K^+ repletion more difficult in acute HF. Upfront use of acetazolamide in adjunct to loop diuretic therapy effectively prevents metabolic alkalosis during decongestion and could be considered for this reason.[32] Early use of mineralocorticoid receptor antagonists is needed to remediate hyperaldosteronism and reduces the risk of hypokalaemia in HF.[70] Finally, hypomagnesaemia increases renal K^+ wasting and impairs cellular uptake of K^+ (through lower activity of the Na^+–K^+–ATPase). Since magnesium losses are increased during diuretic therapy, it makes sense to have a low threshold for magnesium supplementation during decongestive treatment in acute HF.

Preserving the chloride balance

Preventing Cl^- depletion avoids hypochloraemic metabolic alkalosis, plasma volume contraction, and exaggerated neurohumoral activation, allowing better diuretic efficiency to facilitate natriuresis. Cl^- supplements can be provided, with KCl a convenient way to simultaneously fulfil the need for K^+ supplementation as discussed above. Moreover, it is important to realize that K^+ buffers such as citrate or gluconate may actually decrease serum Cl^- levels further to aggravate metabolic alkalosis. However, the earliest reports of Cl^- supplementation date from the'50s and'60s, when mercurial diuretics were commonly used in conjunction with salt restriction and digitalis for patients with congestive HF. In this era, it was found that these measures often became ineffective, but Cl^- supplements could restore diuretic response.[71–74] While seemingly forgotten for a long time, these insights have experienced a revival when Hanberg *et al.*[75] tested thrice daily supplementation with 7 g lysine-Cl^- in 10 stable outpatients with HF under maintenance loop diuretic treatment at a dose ≥80 mg of oral furosemide equivalents. Lysine-Cl^- supplementation was associated with an increase in serum Cl^- levels of 2.2 mmol/L and the majority of participants experienced favourable findings reflecting improved decongestion, such as haemoconcentration, weight loss, and a reduction in natriuretic peptide levels. These data suggest that hypochloraemia in HF may represent more than just a marker of disease severity but may be amenable to therapeutic modification. Two larger trials are currently conducted to explore the usefulness of Cl^- supplementation in contemporary populations with acute (NCT03446651) and chronic HF (NCT03440970).

Interestingly, diuretic agents exerting their effects in the proximal renal tubules have Cl^--preserving characteristics. Acetazolamide, a carbonic anhydrase inhibitor, reduces urinary Cl^- loss by about 5%.[33] In a post-hoc analysis of the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial, upfront use of acetazolamide on top of loop diuretic treatment in acute HF was shown to increase serum Cl^- by ~3 mmol/L within 3 days, thereby effectively preventing loop diuretic-induced hypochloraemia.[33] Since the latter is so common, we recommend

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upfront use of acetazolamide in all patients who are likely to receive multiple doses of loop diuretics. In addition, sodium–glucose cotransporter 2 inhibitors that are part of the guideline-directed medical therapy for all patients with HF, similarly increase serum Cl^- levels (as well as magnesium levels and K^+ levels when depleted), thereby enhancing the effects of other diuretic classes and reducing renal Na^+ avidity through the mechanisms earlier discussed.[76]

Conclusions

This review highlights the critical mismatch between electrolyte and water disturbances in HF and the effects of commonly employed diuretic therapy to treat fluid overload. The role of the three major electrolytes was discussed: Na^+ as an intracellular and interstitial volume buffer, K^+ as the predominant intracellular osmolyte, and Cl^- as the intravascular tonicity regulator. HF is characterized by Na^+ retention that is disproportionate to electrolyte-free water retention, leading to a state of relative dehydration, as well as reduced total body K^+ stores that further exacerbate intracellular dehydration. Diuretic therapy leads to disproportionate excretion of electrolyte-free water, further K^+ depletion and urinary Cl^- excretion that is disproportionate to natriuresis. To produce balanced diuresis and restore homeostasis, strategies such as liberal electrolyte-free water intake, aggressive K^+ and Cl^- supplementation, and upfront use proximal diuretics to preserve the Cl^- balance may be considered, which should be the topic of further randomized studies and trials.

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Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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